

Eye Movement Dysfunction in Schizophrenia: A Heritable Characteristic for Enhancing Phenotype Definition

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The occurrence of ocular motor dysfunction in schizophrenia patients and their first-degree biological relatives is remarkably consistent, suggesting that abnormal smooth pursuit and saccadic oculomotion are heritable characteristics that can be used to identify gene carriers for schizophrenia. Saccadic system dysfunction probably reflects a generalized deficit in prefrontal cortical functioning, rather than a specific deficit in saccade system functioning. Although abnormal smooth pursuit has also been associated with impaired frontal functioning, it is unclear whether these two types of dysfunction arise from the same neural pathology. Therefore, deviant smooth pursuit and saccadic oculomotion may constitute unrelated factors identifying two different types of genetic risk. Alternatively, they may derive from a single risk factor that causes (a) both types of deficits to be expressed together or (b) each type to be expressed separately as pleiotropic manifestations of the underlying genotype. Although a full complement of pursuit and saccade measures has not been examined together in family studies of schizophrenia, there is obvious value in determining how these measures relate to one another in schizophrenia families and whether they can be used in combination to enhance phenotype definition to facilitate the search for schizophrenia susceptibility genes. *J. Am. Med. Genet. (Semin. Med. Genet.) 97:72–76, 2000. © 2000 Wiley-Liss, Inc.*

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INTRODUCTION

At the turn of this century, two researchers working in a psychiatric hospital in New England made the unprecedented observation that patients with dementia praecox had difficulty following an oscillating pendulum with their eyes [Diefendorf and Dodge, 1908].

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This finding went relatively unnoticed for many years, until the early 1970s when the occurrence of eye movement dysfunction (EMD) was once again observed in many individuals afflicted with the disorder that had come to be termed schizophrenia [Holzman et al., 1973]. Since that time, several hundred studies have reported that schizophrenia patients have abnormally high rates of EMD [see Levy et al., 1993 for a narrative review]. Although this robust finding may ultimately yield insights into the pathophysiology of schizo-

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phrenia, scientists have been especially intrigued by consistent observations indicating that the non-psychotic first-degree biological relatives of schizophrenia patients also exhibit EMD. This latter finding suggests that the study of EMD may shed light on the genetic origins of schizophrenia.

EYE MOVEMENT ASSESSMENT

Investigations of EMD in schizophrenia have focused on the smooth pursuit and saccadic eye movement systems. The smooth pursuit system is evoked by slowly moving visual objects, such as a swinging pendulum or bird soaring in the distant sky, and maintains the image of the object on the retina by matching the velocity of the eye with the velocity of the target. The saccadic system generates high velocity eye movements that move the eyes from one position to another. Saccadic eye movements are generally recognized as composed of several subtypes, including voluntary (or intentional), reflexive and spontaneous saccades. Saccades rapidly foveate a target, centering the image on the region of the retina where visual acuity is sharpest. Although saccades are typically elicited by abruptly moving targets, they also arise with targets eliciting smooth pursuit movements to correct position error when the eye lags behind a target in continuous motion. They may also interrupt smooth pursuit tracking, perhaps reflecting a failure of

inhibitory control leading to the production of unnecessary, intrusive saccades. Examples of pursuit and saccadic eye movements are presented in Figure 1.

In experimental studies of oculomotion, infrared reflection and electro-

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oculographic techniques are used to record eye movements in response to different types of computer generated targets. Digitized representations of these recordings can be variously quantified, yielding both global measures of tracking accuracy (i.e., a single score summarizing overall performance) and measures of performance deficit that identify specific deficiencies.

SCHIZOPHRENIA IS CHARACTERIZED BY GLOBAL SMOOTH PURSUIT DYSFUNCTION

Global measures of smooth pursuit tracking accuracy ostensibly include the assessment of eye movements resulting from dysfunction in the smooth pursuit system, the saccadic system, or both. More than one hundred investigations of global smooth pursuit functioning have been conducted with schizophrenia patients, sometimes including their relatives, and almost all have indicated significant impairment in both the patients and their relatives. Figure 1a illustrates how schizophrenia family members fail to reproduce the smooth motion of a sinusoidal target. This smooth pursuit dysfunction is stable over time [Gooding et al., 1994], present during symptom remission [Iacono et al., 1982], and familial [Iacono et al., 1992]. Not all schizophrenia families display signs of EMD [Clementz et al., 1992; Iacono et al. 1992], an observation that is consistent with the possibility that schizophrenia is etiologically

heterogeneous. Other patient groups, such as bipolar patients, have been reported to have smooth pursuit tracking dysfunction as well, but their biological relatives have not, suggesting that globally assessed EMD in bipolar patients may be state, rather than trait, related [Holzman et al., 1984; Iacono et al., 1992].

GLOBAL SMOOTH PURSUIT EMD AS AN ENDOPHENOTYPIC MARKER OF SCHIZOPHRENIA

Could a single gene account for a substantial fraction of the variance in global EMD scores? If it did, it would be reasonable for these scores to comprise two or more distributions composed of those with the expressed gene and those without it. Mixture analysis, a statistical technique that can be used to provide a test of whether continuously distributed data are better fit by a single or two mixing distributions, has suggested that

the EMD scores of schizophrenia patients and their relatives reflect the presence of two mixing distributions [Clementz et al., 1992; Iacono et al., 1992]. Genetic models fit to eye tracking data from schizophrenia family members suggest that a single gene accounts for substantial variance in the expression of the EMD phenotype [Holzman et al., 1988; Grove et al., 1992]. Such results suggest that there are two distinct groups of schizophrenia patients, those with globally poor smooth pursuit and those with intact smooth pursuit functioning. These studies, however, have also shown that patients with intact pursuit may have healthy relatives with EMD [e.g., Holzman et al., 1977; Iacono et al., 1992]. Such findings suggest the presence of pleiotropy (one genotype, multiple seemingly unrelated phenotypic effects) with underlying genetic risk ultimately being expressed as schizophrenia, EMD, or both.

The results of these investigations suggest that EMD, assessed globally, is

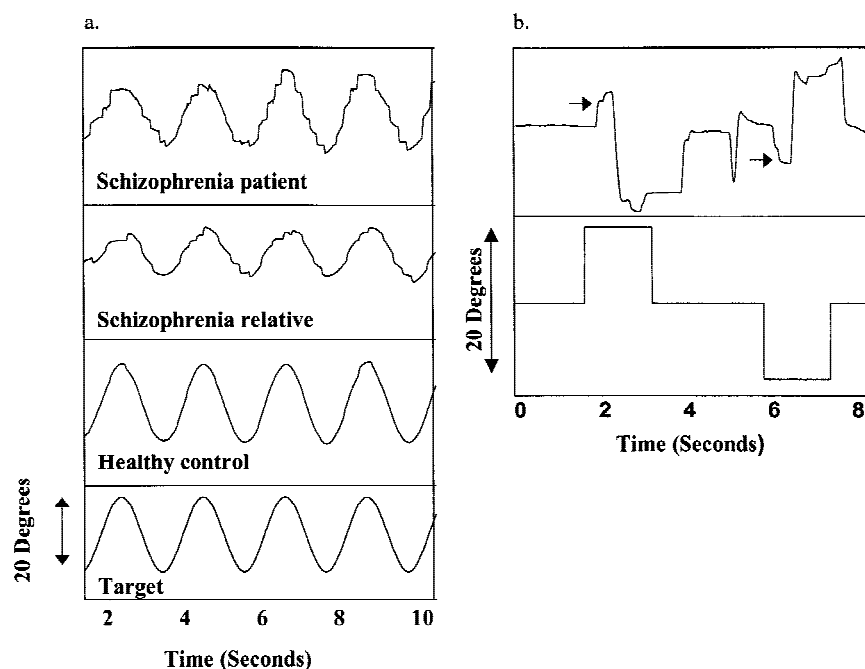


Figure 1. **a:** Smooth pursuit eye movement functioning in a patient with schizophrenia, the first-degree biological relative of a schizophrenia patient, and a healthy control participant. The patient with schizophrenia and the schizophrenia relative have difficulty keeping up with the target and generate frequent saccadic eye movements. The tracking of the healthy control is unimpaired. The target is a 0.4 Hz sinusoidal stimulus traversing 20 degrees of visual angle. **b:** Performance of a schizophrenia patient on two trials of an antisaccade task. The participant is instructed to generate a saccade in the direction opposite that of target motion. At the outset of each trial, the target (lower panel) is at a central fixation corresponding to the center of the display screen. It then appears at a point 10 degrees on either side of central fixation. The record from this patient (upper panel) indicates that he or she failed to inhibit a reflexive saccade to the target (demarcated with arrows), but then quickly corrected the reflexive error, on both trials. Degrees are degrees of visual angle.

an endophenotype of schizophrenia, a phenotypic trait that indexes genetic risk but that can be measured only with a laboratory procedure. Valid endophenotypes identify individuals who carry the gene or genes for a disorder, even though the individuals may be otherwise asymptomatic. Because the vast majority of schizophrenia families contain only one clinically affected member, having a means for identifying gene carriers in such families greatly increases the power to detect linkage and identify etiologically relevant genes.

THE NATURE OF THE SMOOTH PURSUIT ANOMALY

Research aimed at identifying the CNS mechanisms underlying EMD has lagged behind that devoted to investigating its properties as an endophenotype. Because the neuro-ophthalmology of the ocular motor system, especially the saccadic system, is relatively well understood, scientists have attempted to parse the smooth pursuit tracking response into components characterized by the presence of smooth eye movements and saccades. These components have been quantified using methods borrowed from neuro-ophthalmology and subtyped based on their apparent function. One such pursuit measure is gain, which reflects the ratio of eye velocity to target velocity during epochs when the eyes follow the target smoothly. Individuals whose eyes cannot keep up with the target have low gain pursuit. Most investigations of gain have indicated that patients with schizophrenia and their relatives exhibit marked difficulties maintaining an eye velocity that matches the velocity of the target during a smooth pursuit task. Rather, their eyes tend to lag behind the target, and they generate frequent saccades [e.g., Sweeney et al., 1994].

Other measures are derived from the characteristics of saccades that appear during pursuit. Although there is some variability in the findings, the bulk of the evidence suggests that the saccades generated by schizophrenia patients during smooth pursuit are correc-

tive rather than intrusive. That is, when the smooth pursuit system is unable to match the velocity of the target, it seems that the saccadic system generates a corrective saccade that serves to bring the position of the eyes back to the target. Thus, the abundant saccades exhibited by schizophrenia patients do not seem to be extraneous, intrusive eye movements, as would occur if there were a failure to inhibit the saccadic system during pursuit. Additional work suggests that patients with schizophrenia also have difficulty initiating smooth pursuit eye movements at the beginning of the task, suggesting that there may be a dysfunction in the neural mechanisms that control the initiation of smooth pursuit [e.g., Clementz and McDowell, 1994]. Thus, difficulties in the initiation and maintenance of smooth pursuit seem to characterize the smooth pursuit tracking of patients with schizophrenia [although for an alternative interpretation, see Clementz, 1998].

SACCADIC SYSTEM EMD

Most investigations of saccadic system functioning in schizophrenia patients and their relatives have occurred within the context of smooth pursuit tasks. Recently, however, investigators have turned their attention to the study of voluntary and reflexive saccades occurring in tasks specifically designed to elicit them. Although relatively little is known about the neural control of spontaneous saccades that occur during smooth pursuit, great progress has been made in mapping the complex neural circuits underlying other types of saccadic eye movements. Intentional or voluntary saccades are volitional eye movements that are internally triggered by an individual to achieve a goal (e.g., examine the features of a landscape painting). In contrast, reflexive visually guided saccades are triggered externally and, as their name implies, as a reflexive response to a suddenly appearing stimulus.

Two subtypes of volitional saccades have been frequently investigated in schizophrenia patients. The first, the antisaccade, is elicited by a task that re-

quires that the participant generate a saccade in the direction opposite that of target motion. Schizophrenia patients and their biological relatives have demonstrated a replicated deficiency in their ability to inhibit reflexive saccades to the target [Clementz et al., 1994; Katsanis et al., 1997; McDowell and Clementz, 1997; Ross et al., 1998; Curtis et al., 1999; McDowell et al., 1999; see Fig. 1b]. Indeed, recent work in our laboratory has indicated that the biological relatives of schizophrenia patients who show antisaccade EMD have EMD themselves. In contrast, patients who do not have increased rates of error tend to have relatives who also perform well [Curtis et al., 1999, 2000; see also Crawford et al., 1998]. Such results suggest that antisaccade EMD is familial and that it may, just as smooth pursuit EMD seems to, identify the healthy non-psychotic relatives who carry the genetic predisposition for schizophrenia.

Antisaccade EMD may identify relatives who carry the genetic predisposition for schizophrenia.

The second type of volitional saccade is the memory-guided saccade evoked by an oculomotor delayed response task. This task requires the participant to generate saccades, after a period of delay and upon a cue, that are directed toward the remembered location of a target. Relatively few studies have been conducted with schizophrenia patients and this task, but those that have indicate that schizophrenia patients, compared to healthy controls, are slow to move their eyes toward the remembered target once the cue to generate a saccade has been issued. In addition, schizophrenia patients generate frequent inappropriate reflexive saccades to the initial target, and frequent anticipatory eye movements during the delay between the initial target and the cue to look to the remembered location of the initial target [e.g., McDowell and Clementz, 1996.] The biological relatives of schizophrenia patients show

similar deficits [e.g., Clementz, 1998]. In contrast to the results of these studies of volitional saccades, investigations of visually guided reflexive saccades have reported that schizophrenia patients do not differ from healthy participants in saccade latencies or amplitudes [e.g., Clementz et al., 1994].

PREFRONTAL CORTEX AND EMD

Various lines of evidence suggest that the EMD of schizophrenia patients may stem from an underlying dysfunction of the prefrontal cortex. For instance, although an intact dorsolateral prefrontal cortex may not be essential to good smooth pursuit tracking [Gooding et al., 1999], impaired pursuit is associated with impairments on neuropsychological tasks putatively sensitive to frontal cortex functioning [e.g., Katsanis and Iacono, 1991], including tests of working memory [e.g., Park and Holzman, 1993; Snitz et al., 1999] that are both sensitive to dorsolateral prefrontal cortical functioning and performed poorly by the relatives of schizophrenia patients [Park et al., 1995; Conklin et al., in press]. Moreover, positron emission tomography has shown that schizophrenia relatives with pursuit EMD, compared to those with normal tracking and nonpsychiatric comparison subjects, fail to activate the frontal eye fields during pursuit following tasks [O'Driscoll et al., 1999]. The prefrontal cortex is one component of the saccadic system as invoked by memory guided saccade and antisaccade paradigms. Noting that visually guided reflexive saccades are largely normal in schizophrenia patients, Clementz [1998] has suggested that poor performance on memory guided and antisaccade tasks is not indicative of deficits unique to the saccadic system, and that instead, it represents a deficiency in prefrontal cortical functioning. Taken in the aggregate, this intriguing set of findings suggests that patients with schizophrenia and their relatives have multiple forms of EMD, perhaps indicating a prefrontal cortical dysfunction. The available evidence, however, leaves unclear whether smooth pursuit EMD could stem

from the same putative prefrontal cortical dysfunction as saccadic EMD.

EXPANDING THE ENDOPHENOTYPE

Endophenotype identification can aid the elucidation of the genetic transmission of schizophrenia, for example, by providing an alternative to the diagnosis of schizophrenia for use in linkage studies. The only study to date that has employed EMD in a linkage analysis used a smooth pursuit task. Arolt et al. [1996] reported linkage of pursuit EMD to chromosome 6. These results, however, though promising, have yet to be replicated, and questions have been raised about the likelihood that EMD will ultimately prove beneficial in such studies [Faraone et al., 1995] because some of its manifestations are relatively common in nonschizophrenic individuals (e.g., the prevalence of global EMD is sometimes estimated at 8% in normals).

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An alternative to relying on a single endophenotype to identify genetic risk is to combine endophenotypes for this purpose or to create a composite, multivariate phenotype. Although requiring the simultaneous presence of multiple deviations may reduce the proportion of schizophrenia family members identified as gene carriers, such an approach would still be advantageous if the multivariate phenotype were extremely rare in individuals who neither have the diagnosis nor are related to someone who does. Despite the obvious utility of combining different eye movement measures derived from pursuit and saccadic eye tracking tasks in this way, investigations of smooth pursuit and saccadic system functioning have, by and large, been

conducted independently. That is, no investigators have attempted to examine the relationships among a full complement of these specific deficits in a single sample of schizophrenia patients and their relatives.

Thus, important questions remain regarding how the smooth pursuit and saccadic system deficits are related, and whether these deficits could be manifestations of the same genetic mechanism, one that perhaps plays a role in the functioning of the prefrontal cortex. Could smooth pursuit and saccadic system deficits reflect pleiotropic manifestations of the same genotype in that the presence of one characteristic in one family member increases the risk of the other characteristic in another member of the same family? Do the smooth pursuit and saccadic system deficits tend to identify the same patients with schizophrenia, or are largely non-overlapping groups of patients identified by each deficit? That is, do the deficits co-aggregate in schizophrenia patients? Furthermore, do they tend to co-aggregate in the biological relatives of the schizophrenia patients? If so, do the biological relatives of patients with combined deficits exhibit them at a rate higher than the relatives of the schizophrenia patients without the deficits?

Until these questions are answered, it is unclear how smooth pursuit deficiencies are related to saccadic system difficulties, and therefore whether saccadic system deficits mark the same putative genetic subtype of schizophrenia as smooth pursuit dysfunction. If the answers to one or more of these questions is yes, then the saccadic system deficits could be combined with global pursuit tracking deficits to identify a single variant of genetic risk for schizophrenia. If these deficits arise largely independently of one another, they may assist in the identification of different variants. Either way, answers to these questions will enhance the likelihood that EMD will play a substantial role in elucidating the genetic origins of schizophrenia.

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